

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US05/002229

International filing date: 19 January 2005 (19.01.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/537,622
Filing date: 20 January 2004 (20.01.2004)

Date of receipt at the International Bureau: 03 March 2005 (03.03.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

1287957

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

February 22, 2005

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: 60/537,622

FILING DATE: *January 20, 2004*

RELATED PCT APPLICATION NUMBER: *PCT/US05/02229*



Certified by

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

012004

22763 U.S. PTO

PTO/SB/16 (06-03)


Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV 357959858 US

INVENTOR(S)					
Given Name (first and middle [if any])		Family Name or Surname		Residence (City and either State or Foreign Country)	
MERRITT B.		ANDRUS		186 N. 980 E., LINDON, UT 84042	
Additional inventors are being named on the _____ separately numbered sheets attached hereto					
TITLE OF INVENTION (500 characters max)					
RESVERATROL ANALOG COMPOUNDS AND METHOD FOR PRODUCING SAME					
Direct all correspondence to:			CORRESPONDENCE ADDRESS		
<input type="checkbox"/> Customer Number OR <input type="checkbox"/> Firm or Individual Name			 26582		
Holland & Hart LLP					
Address			555 17 th Street		
Address			Suite 3200		
City			State	Colorado	ZIP
Denver					80202
Country			Telephone	Fax	
USA					303-295-8261
ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/>	Specification Number of Pages		12	<input type="checkbox"/>	CD(s), Number
<input checked="" type="checkbox"/>	Drawing(s) Number of Sheets		6	<input type="checkbox"/>	Other (specify)
<input type="checkbox"/>	Application Data Sheet. See 37 CFR 1.76				
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT					
<input type="checkbox"/>	Applicant claims small entity status. See 37 CFR 1.27.				FILING FEE AMOUNT (\$)
<input checked="" type="checkbox"/>	A check or money order is enclosed to cover the filing fees.				160.00
<input checked="" type="checkbox"/>	The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number:				082623
<input type="checkbox"/>	Payment by credit card. Form PTO-2038 is attached.				
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.					
<input checked="" type="checkbox"/>	No				
<input type="checkbox"/>	Yes, the name of the U.S. Government agency and the Government contract number are: _____				


17548 U.S. PTO
60/537622

012004

[Page 1 of 2]

Respectfully submitted,

SIGNATURE



TYPED or PRINTED NAME CHRISTOPHER L. WIGHT

TELEPHONE (801) 595-7823

Date: 1/20/04

REGISTRATION NO.

31,680

(if appropriate)

Docket Number:

49506.0002

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop Provisional Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

22763 U.S. PTO
012004

Express Mail Label No. EV 357959858 US

IN THE UNITED STATES RECEIVING OFFICE
UNDER THE PATENT COOPERATION TREATY

In re Provisional Application of:

BRIGHAM YOUNG UNIVERSITY,
TECHNOLOGY TRANSFER OFFICE

Application No.: Unknown

Filing Date: Herewith

For: RESVERATROL ANALOG COMPOUNDS AND
METHOD FOR PRODUCING SAME

Attorney File No.: 49506.0002

Mail Stop Provisional Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING BY EXPRESS MAIL

Sir:

The undersigned hereby certifies that the enclosed

1. Provisional Application for Patent Cover Sheet; w/ \$160 check
2. Specification (12 pages);
3. Drawings (6 pages); and
4. Return Card;

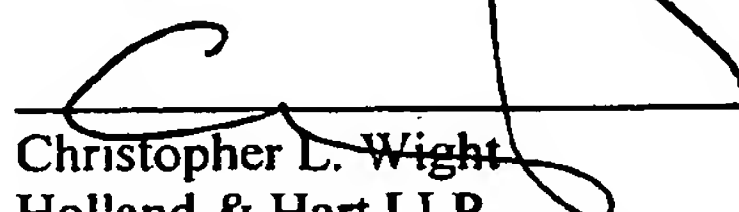
and this Certificate of Mailing by Express Mail relating to the above application, were deposited as "Express Mail", Mailing Label No. EV 357959858 US with the United States Postal Service, addressed to Mail Stop Provisional Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on 20 January 2004.

20 January 2004



Mailer

20 January 2004



Christopher L. Wight
Holland & Hart LLP
60 East South Temple, Suite 2000
Salt Lake City, UT 84111
Telephone: (801) 595-7823
Facsimile: (801) 364-9124

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

**PROVISIONAL APPLICATION
FOR LETTERS PATENT**

Resveratrol Analog Compounds and Method for Producing Same

INVENTOR:

Merritt B. Andrus

PREPARED BY:

**HOLLAND & HART LLP
60 EAST SOUTH Temple, Suite 2000
SALT LAKE CITY, UTAH 84111**

ATTORNEY DOCKET NO. 49506.0002

Resveratrol Analog Compounds and Method for Producing Same

The compositions of the present invention are analogs of resveratrol, in particular esters of resveratrol.

The resveratrol (3,5,4'-trihydroxy-*trans*-stilbene) esters of the present invention are characterized in that they comprise least one ester group of formula —O—CO—R at one or more of the 3, 5 and 4' positions, wherein R represents an alkyl radical with at least two carbon atoms, linear or branched, saturated or unsaturated, an aryl radical, aralkyl or aralkylene, alkylene with 0 to 10 carbon atoms, saturated or unsaturated, and/or 1 arylene radical having 1 to 3 rings and/or a heterocyclic radical, and the diastereoisomers of these units.

These compositions can be stored over a long period without alteration.

In a particular embodiment, R represents a saturated or unsaturated fatty acid radical.

In the case of an unsaturation, the double bonds are advantageously *cis*, which corresponds to the most frequent case found in the natural products. With products obtained more particularly by synthesis or hemisynthesis, the bonds are *trans*.

Fatty acid derivatives which are suitable for the implementation of the invention include: butyric C4:O; valeric, C5:O; hexanoic, C6:O; sorbic, C6:2(n-2); lauric C12:O; palmitic C16:O; stearic, C18:O; oleic, C18:1(n-9); linoleic, C18:2(n-6); linolenic, C18:3(n-6); α -linolenic, C18:3(n-3); arachidonic, C20:4(n-3); eicosapentaenoic C20:5(n-3); and docosahexanoic, C22:6(n-3). The C16 and more fatty acids are particularly appropriate as regards cosmetic uses. These fatty acids are extracted, for example, from microalgae.

In another embodiment, R represents an aryl group.

In yet another embodiment, R represents an aralkyl or aralkylene group, the alkyl or alkylene group being more particularly C1 to C8, in particular C1 to C4. In particular the benzyl or styryl group can be utilized.

Examples

Air and moisture sensitive reagents were introduced via dry syringe or cannula. Toluene, xylene, pyridine, ethyl acetate, and N-methyl morpholine were distilled from CaH_2 . DMF were dried by storage over 4Å Molecular sieves. Reagents were purchased from Aldrich and Lancaster. Flash chromatography was carried out using 60-230 mesh silica gel. Radical chromatography was performed using 1, 2, and 4 mm plates loaded with 230-400 mesh PF-254 gypsum bound silica. Analytical thin-layer chromatography (TLC) was performed with Merck silica gel 60 F₂₅₄, 0.25 mm pre-coated TLC plates. TLC plates were visualized using UV₂₅₄. All ^1H NMR spectra were obtained with 300 Varian spectrometers using TMS (0.00ppm), Chloroform (7.26 ppm), or acetone- d_6 (2.05 ppm) as an internal reference. Signals are reported as m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), and bs (broad singlet). ^{13}C NMR were obtained with 75 MHz Varian spectrometer using TMS (0.0 ppm), Chloroform (77.2 ppm), or acetone- d_6 (30.6 ppm) as the internal standard. Mass spectra data (HRMS, EI) were obtained from the Brigham Young University mass spectrometry facility.

Preparation of 3,5-bis(methoxymethoxy)benzoic acid.

A flame dried flask was charged with dry DMF (75mL) and 60% oil dispersion NaH (3.8 g, 95 mmol). A solution of 3,5-dihydroxybenzoic acid (4.6 g, 30 mmol) in DMF (25mL) was added dropwisely over 20 minutes. The mixture was allowed to stir for one hour under N_2 . MOMCl (7.5 mL, 100 mmol) was added slowly so that the inner temperature did not exceed 50°C. After 30 hours, the insoluble material was filtered off and the filtrate was concentrated to an oil residue, which was partitioned between benzene and water. The water layer was extracted with benzene for another three times. The combined benzene extracts was dried by Na_2SO_4 and concentrated to a pale yellow oil, which was dissolved in 50 mL methanol. 2N aqueous NaOH (25 mL, 50 mmol) was added and the mixture was stirred for three hours. The mixture was concentrated and dissolved in 30mL water. The aqueous solution was washed with benzene and acidified with 10% aqueous HCl. The white solid precipitated out was filtered and washed with water and dried to give 6.6g (91%) product, which can be further purified by

recrystallization from AcOEt-hexane. Data are: ^1H NMR (CDCl_3 , 300 MHz) δ 7.44 (d, 2H), 6.98 (t, 1H), 5.21 (s, 4H), 3.50 (s, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 170.9, 158.4, 131.4, 111.5, 110.7, 94.7, 56.4; mp = 129-130 °C; HRMS (EI^+) found 242.0796 M^+ , calcd 242.0790 for $\text{C}_{11}\text{H}_{14}\text{O}_6$.

Preparation of 3,5-bis(methoxymethoxy)benzoic chloride.

A stock solution was prepared by dissolving benzotriazole (1.49 g, 0.0125 mmol), thionyl chloride (0.91 mL, 0.0125 mmol) in 8.0 mL DCM. Reaction was carried out by adding the stock solution intermittently into a stirred solution of 3,5-bis(methoxymethoxy)benzoic acid (2.42 g, 10 mmol) in 200 mL DCM. Before the addition was complete, benzotriazole hydrochloride started precipitating out as a white solid. The mixture was stirred for another ten minutes. After filtration, the filtrate was stirred with $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ (5g) to destroy excess thionyl chloride. The white solid was filtered off and the filtrate concentrated to give 2.5g (97%) crude product, which was used for the next step without further purification. Data are: ^1H NMR (CDCl_3 , 300 MHz) δ 7.44 (d, 2H), 7.04 (t, 1H), 5.20 (s, 4H), 3.49 (s, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 168.1, 158.5, 135.3, 112.6, 111.9, 94.7, 56.4; HRMS (EI^+) found 260.0465 M^+ , calcd 260.0452 for $\text{C}_{11}\text{H}_{13}\text{O}_5\text{Cl}$.

Preparation of 3,5-bis(methoxymethoxy)-4'-acetoxy stilbene.

A 50 mL round bottom flask was charged with p-xylene (20 mL), $\text{Pd}(\text{OAc})_2$ (22.5 mg, 0.1 mmol), 1,3-bis-(2,6-diisopropylphenyl) imidazolinium chloride (42.7 mg, 0.1 mmol), 3,5-bis(methoxymethoxy)benzoic chloride (2.42 g, 10 mmol), 4-acetoxystyrene (1.94 g, 12 mmol), and N-methyl morpholine (1.38 g, 12 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to room temperature and EtOAc was added and filtered. The filtrate was washed with brine and dried over Na_2SO_4 . Then it was filtered and purified via flash chromatography and gave the product (2.1 g, 59%) as a white solid. Data are: ^1H NMR (CDCl_3 , 300 MHz) δ 7.48 (d, 2H), 7.08-6.93 (m, 4H), 6.86 (d, 2H), 6.66 (t, 1H), 5.19 (s, 4H), 3.50 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 169.5, 158.7, 150.3, 139.5, 135.0, 128.7, 128.5, 127.6, 121.9, 108.0, 104.5, 94.6, 56.2, 21.2; HRMS (EI^+) found 358.1409 M^+ , calcd 358.1416 for $\text{C}_{20}\text{H}_{22}\text{O}_6$.

Preparation of 3,5-dihydroxy-4'-acetoxy stilbene.

To a solution of 5-bis(methoxymethoxy)-4'-acetoxy stilbene (0.358 g, 1 mmol) in dry DCM (50mL) and dry CH₃CN (50mL) was added NaI (1.8 g, 24 mmol) and freshly distilled (1.52 g, 24mmol). The mixture was stirred under argon for 15 minutes. The solution was diluted with DCM (50mL) and washed with a freshly aqueous saturated solution of Na₂S₂O₄ (3×40mL) and saturated NaHCO₃, and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash column and gave 0.20 g product (72%). Data are: ¹H NMR (Aceton-d₆, 300 MHz) δ 8.25 (s, 1H), 7.60 (m, 2H), 7.13-7.08 (m, 4H), 6.59 (d, 2H), 6.32 (t, 1H), 2.25 (s, 3H); ¹³C NMR (Aceton-d₆, 75 MHz) δ 169.7, 159.7, 151.4, 140.4, 136.0, 130.0, 128.3, 128.3, 123.0, 106.1, 103.3, 21.1; HRMS (EI⁺) found 270.0889 M⁺, calcd 270.0892 for C₁₆H₁₆O₄.

Preparation of 3,5-diacetoxybenzoic acid chloride.

To a solution of 3,5-diacetoxybenzoic acid (7.71 g, 50 mmol) in EtOAc (110 mL) were added acetic anhydride (12.25 mL, 130 mmol) and pyridine (8.08 mL, 100mmol) in an ice-water bath under a nitrogen atmosphere. The mixture was stirred at 0 °C for 40 min and then stirred at ambient temperature for 4 h. 98% Formic acid (2.36 mL, 60 mmol) was added and the resulting mixture was stirred for 1 h. Then, it was poured into water and extracted with EtOAc. The organic phase was washed with water and brine, dried over Na₂SO₄, filtered, and evaporated in vacuo. Purification of the residue via recrystallization from n-heptane/EtOAc provided 3,5-diacetoxybenzoic acid (8.97 g, 75.3%) as a white solid. Data are: ¹H NMR (CDCl₃, 300 MHz) δ 12.1 (bs, 1H), 7.73 (d, 2H), 7.21 (t, 1H), 2.32 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 170.4, 169.0, 151.2, 131.5, 121.3, 121.0, 21.2; mp = 161-162 °C; HRMS (EI⁺) found 238.0475 M⁺, calcd 238.0477 for C₁₁H₁₀O₆; Anal. Calcd for C₁₁H₁₀O₆: C, 55.47; H, 4.23. Found: C, 55.62; H, 4.37.

To a mixture of 3,5-diacetoxybenzoic acid (8.00 g, 33.59 mmol) and dimethylformamide (5 drops) added fresh distilled thionylchloride (16 mL). The mixture was stirred for 15 min under nitrogen atmosphere at ambient temperature. Then it was refluxed for 2 h at 80 °C in a hot water bath. The excess thionyl chloride was evaporated

in vacuo and toluene was added. Insoluble yellow solid was discarded. The toluene was evaporated in vacuo and gave 3,5-diacetoxybenzoic acid chloride (8.23g, 95.5%) as a white solid. Data are: ^1H NMR (CDCl_3 , 300 MHz) δ 7.75 (d, 2H), 7.29 (t, 1H), 2.34 (s, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 168.8, 167.0, 151.4, 135.3, 122.8, 122.0, 21.2; mp = 89.5-91 °C; HRMS (EI^+) found 256.0130 M^+ , calcd 256.0139 for $\text{C}_{11}\text{H}_9\text{O}_5\text{Cl}$; Anal. Calcd for $\text{C}_{11}\text{H}_9\text{O}_5\text{Cl}$: C, 51.48; H, 3.53. Found: C, 51.60; H, 3.68.

Preparation of 4-chloroacetoxystyrene.

To a flask was charged with 4-acetoxystyrene (10 g, 61.73 mmol), methanol (30mL), and KOH (0.125 g, 2.23mmol), and 1 drop of water. After the mixture was stirred for 5 minutes under N_2 , the temperature was raised to 65°C. The mixture was stirred for 1.5 h and then cooled to room temperature. Acetic acid (0.144 g, 2.44mmol) in methanol (0.5mL) was added slowly over 5 min. The mixture was stirred for another 5 min and then concentrated. The residue was dissolved in toluene and filtered. The filtrate was cooled to -78°C and the 4-hydroxystyrene was precipitated, filtered and dried to give 4.5 g product (60%).

To a solution of 4-hydroxystyrene (1.22 g, 10 mmol) in ethyl ether 140 mL was added chloroacetic chloride (2.26 g, 20 mmol) and Et_3N (1.62 g, 16 mmol). After 2 h, the mixture was washed with NaHCO_3 and water. The ether solution was dried by Na_2SO_4 and concentrated. After purification by flash column, the 4-chloroacetoxystyrene (1.8 g, 92%) was obtained.

Preparation of 3,5-diacetoxy-4'-chloroacetoxystyrene.

A 10 mL round bottom flask was charged with p-xylene (4 mL), $\text{Pd}(\text{OAc})_2$ (4.5 mg, 0.02 mmol), 1,3-bis-(2,6-diisopropylphenyl) imidazolium chloride (8.6 mg, 0.02 mmol), 3,5-diacetoxybenzoic acid chloride (0.7695 g, 3 mmol), 4-chloroacetoxystyrene (0.393 g, 2 mmol), and N-methyl morpholine (0.276 g, 2.4 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to room temperature and EtOAc was added and filtered. The filtrate was washed with brine and

dried over Na_2SO_4 . Then it was filtered and purified via flash chromatography and gave the product (0.54 g, 69.4%) as a white solid.

Preparation of 3,5-diacetoxy-4'-hydroxy stilbene.

A solution of 3,5-diacetoxy-4'-chloroacetoxy stilbene (0.388 g, 1 mmol) in 50% aqueous pyridine, which was adjusted to pH 6.7 with hydrochloric acid, was stirred for 6 h at room temperature. The mixture was concentrated and diluted with EtOAc. The mixture was washed with 1 N aqueous HCl, saturated NaHCO_3 and water. Then the EtOAc solution was dried and concentrated. After purification by chromatron, the product (0.28 g, 90%) was obtained.

Preparation of 3-acetoxy-5-hydroxybenzoic acid.

To 3,5-dihydroxybenzoic acid (20 g, 129 mmol) added NaOH (15.6 g, 390 mmol) in 100 mL water. After the mixture was cooled to 0°C , Ac_2O (13.2 g, 129 mmol) was added. The solution was stirred for 40 min and then acidified with 10% H_2SO_4 at 0°C . The precipitate was filtered and washed with cold water. The crude product can be recrystallized from water to give 3-acetoxy-5-hydroxybenzoic acid (15.2 g, 60%).

Preparation of 3-acetoxy-5-levulinoxy-benzoic acid.

To a solution of 3-acetoxy-5-hydroxybenzoic acid (2.45 g, 12.5 mmol) in CH_2Cl_2 (25 mL) added levulinic anhydride (5.4 g, 25 mmol) and pyridine (1.22 mL, 15 mmol) at 0°C . The mixture was stirred at 0°C for another 0.5 h and then was allowed to warm to room temperature. After 3 h, 98% formic acid was added and stirred for 1 h. The mixture was washed with 1 N HCl, saturated NaHCO_3 and water. Then it was dried by Na_2SO_4 and concentrated. The crude product was purified by flash column and give 3-acetoxy-5-levulinoxy-benzoic acid (3.52 g, 96%).

Preparation of 3-acetoxy-5-levulinoxy-benzoic chloride.

A stock solution was prepared by dissolving benzotriazole (1.49 g, 0.0125 mmol), thionyl chloride (0.91 mL, 0.0125 mmol) in 8.0 mL DCM. Reaction was carried out by adding the stock solution intermittently into a stirred solution of 3-acetoxy-5-levulinoxy-

benzoic acid (2.94 g, 10 mmol) in 200ml DCM. Before the addition was complete, benzotriazole hydrochloride started precipitating out as a white solid. The mixture was stirred for another ten minutes. After filtration, the filtrate was stirred with $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ (5g) to destroy excess thionyl chloride. After concentration, the residue was extracted by hot dry hexane several times and recrystallized from hexane to give 3-acetoxy-5-levulinoxy-benzoic chloride (1.4 g, 45%).

Preparation of 3,4'-diacetoxy-5-levulinoxystillbene.

A 25 mL round bottom flask was charged with p-xylene (6 mL), $\text{Pd}(\text{OAc})_2$ (6.9 mg, 0.03 mmol), 1,3-bis-(2,6-diisopropylphenyl) imidazolinium chloride (12.9 mg, 0.03 mmol), 3-acetoxy-5-levulinoxy-benzoic chloride (0.936 g, 3 mmol), 4-acetoxystyrene (0.583 g, 3.6 mmol), and N-methyl morpholine (0.42 g, 3.6 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to room temperature and EtOAc was added and filtered. The filtrate was washed with brine and dried over Na_2SO_4 . Then it was filtered and purified via flash chromatography and gave the product (0.86 g, 70%) as a white solid.

Preparation of 3,4'-diacetoxy-5-hydroxystillbene.

A solution of 3,4'-diacetoxy-5-levulinoxystillbene (0.72 g, 1.75mmol) in THF (5 mL) was added a solution of Na_2SO_3 and $\text{Na}_2\text{S}_2\text{O}_5$ (0.26 g, 2.1 mmol and 0.1 g, 0.53 mmol) in water (5 mL). The reaction mixture was stirred for 9 h at room temperature under N_2 . Then the mixture was poured into water and extracted with ethyl acetate three times and dried over Na_2SO_4 . The solvent was removed under reduced pressure and purified by chromatron to give 3,4'-diacetoxy-5-hydroxystillbene (0.40 g, 73%).

Preparation of 4-levulinoxystyrene.

A flame dried flask was charged with dioxane (120 mL), 4-hydroxystyrene (3.66 g, 30 mmol), levulinic acid (6.97 g, 60 mmol), DCCI (12.39 g, 60 mmol), DMAP (300 mg). The mixture was stirred under N_2 for 3.5 h. the mixture was washed with water, dried over Na_2SO_4 , concentrated under reduced pressure and purified by flash column to give 4-levulinoxystyrene (5.9 g, 90%).

Preparation of 3-acetoxy-4',5-dilevulinoxystillbene.

A 25 mL round bottom flask was charged with p-xylene (6 mL), Pd(OAc)₂ (6.9 mg, 0.03 mmol), 1,3-bis-(2,6-diisopropylphenyl) imidazolinium chloride (12.9 mg, 0.03 mmol), 3-acetoxy-5-levulinoxy-benzoic Chloride (0.936 g, 3 mmol), 4-levulinoxystyrene (0.786 g, 3.6 mmol), and N-methyl morpholine (0.42 g, 3.6 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to room temperature and EtOAc was added and filtered. The filtrate was washed with brine and dried over Na₂SO₄. Then it was filtered and purified via flash chromatography and gave the product (1.0 g, 72%) as a white solid.

Preparation of 3,4'-diacetoxy-5-hydroxystillbene.

A solution of 3-acetoxy-4',5-dilevulinoxystillbene (0.47 g, 1.0 mmol) in THF (3 mL) was added a solution of Na₂SO₃ and Na₂S₂O₅ (0.30 g, 2.4 mmol and 0.11 g, 0.6 mmol) in water (3 mL). The reaction mixture was stirred for 7 h at room temperature under N₂. Then the mixture was poured into water and extracted with ethyl acetate three times and dried over Na₂SO₄. The solvent was removed under reduced pressure and purified by chromatron to give 3,4'-diacetoxy-5-hydroxystillbene (0.19 g, 70%).



Pergamon

SCIENCE @ DIRECT®

Tetrahedron Letters 44 (2003) 4819–4822

TETRAHEDRON
LETTERS

Synthesis of resveratrol using a direct decarbonylative Heck approach from resorcylic acid

Merritt B. Andrus,* Jing Liu, Erik L. Meredith and Edward Narthey

Brigham Young University, Department of Chemistry and Biochemistry, C100 BNSN, Provo, UT 84602-5700, USA

Received 4 February 2003; revised 1 May 2003; accepted 5 May 2003

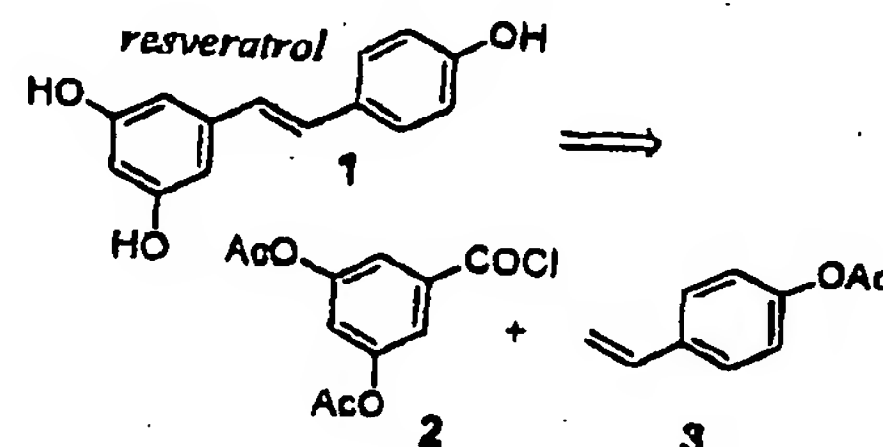
Abstract—The phytoalexin resveratrol has been made using a decarbonylative Heck reaction. The acid chloride derived from 3,5-dihydroxybenzoic acid was coupled with 4-acetoxystyrene in the presence of palladium acetate and *N,N*-bis-(2,6-diisopropyl-phenyl)dihydroimidazolium chloride to give the substituted stilbene in 73% yield as the key step. © 2003 Published by Elsevier Science Ltd.

Phenolic secondary metabolites from plants have recently been shown to possess powerful specific effects against various diseases. These include the epicatechins, from green tea and genistein, from soy beans that prevent tumor formation and osteoporosis.¹ In spite of its simple structure, resveratrol, a stilbene phytoalexin found in grape skins and other berries including peanuts, has turned out to be a true 'Swiss army knife' molecule.² We now report an efficient, direct route to resveratrol **1** starting with inexpensive resorcylic acid (3,5-dihydroxybenzoic acid) using a palladium-catalyzed decarbonylative Heck coupling reaction.

Growing evidence has demonstrated that resveratrol at reasonable dietary concentrations plays an important role in mitigating numerous and diverse human pathological processes including inflammation, atherosclerosis, and carcinogenesis. Specific properties include antioxidant, radical scavenging activity,³ cyclooxygenase inhibition, lipid modification,⁴ platelet aggregation inhibition and vasodilation,⁵ inhibition of tumor initiation, promotion, and progression,⁶ neuroprotection,⁷ and antiviral activity.⁸ Resveratrol is thought to be the causative agent of the 'French paradox,' the molecule most responsible for the Mediterranean diet effect where high fat intake coupled with moderate wine consumption leads to abnormally low rates of heart disease and cancer.⁹

In spite of its wide range of activity, the mechanistic basis for resveratrol's *in vivo* activity remains unclear.¹⁰

Many studies point to its ability to function as a cellular antioxidant, while others demonstrate the inhibition of signaling kinases. In addition to its potential as a tool to study protein signaling, it also may serve as a therapeutic lead, a disease preventative dietary supplement,¹¹ or as a topical treatment.¹² Isolation from plant sources in pure form is not efficient, as reported from dried *Cassia g. Rich* (30 mg/kg)⁶ or from dried grape skins (92 mg/kg).¹³ The majority of the published synthetic routes rely on Wittig and Horner-Emmons couplings that give mixtures of olefin isomers and require 7–8 steps.¹⁴ Most routes use methyl or benzyl ether protecting groups that require the use of boron tribromide or other inconvenient reagents for removal. A palladium catalyzed Heck-based route has been reported that utilized a costly starting material, 3,5-dihydroxybenzaldehyde, together with a Wittig reaction to form the styrene coupling partner.¹⁵ Recently, a vinylsilane Heck based coupling route using halogenated benzene substrates has been reported that uses methyl ether protecting groups.¹⁶ The route now reported involves only four steps from inexpensive



Scheme 1.

* Corresponding author. Fax: +1-801-422-8171; e-mail: mbandrus@chem.byu.edu

4810

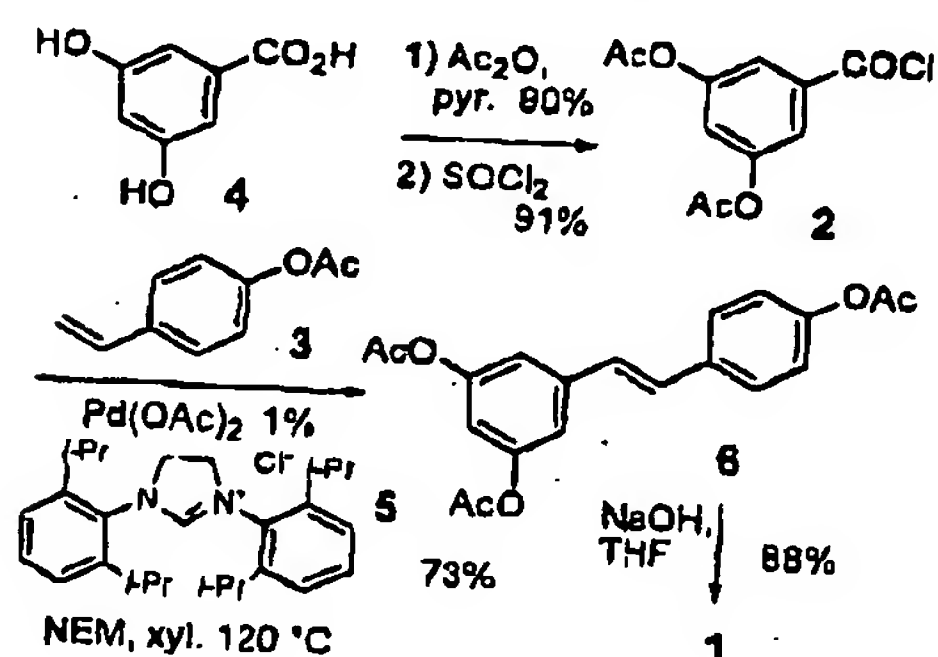
M. B. Andrus et al. / Tetrahedron Letters 44 (2003) 4819-4822

resorcylic acid, converted to its acid chloride 2,¹⁷ and 4-acetoxystyrene 3 (Scheme 1). A novel decarbonylative Heck reaction catalyzed by palladium acetate with an imidazolium carbene-type ligand is used too for stilbene formation. The hydroxyls are conveniently protected as acetate esters which are easily removed with hydroxide. An improved Horner-Emmons route using a diisopropyl phosphonate is also reported.

Resorcylic acid 4 (~\$25/100 g) was reacted with 5 equiv. of acetic anhydride in pyridine to give the protected acid (mp 161°C), following treatment with aqueous formic acid and recrystallization, in 90% isolated yield (Scheme 2). Use of 2.6 equiv. of acetic anhydride gave a reduced yield of 75%. Thionyl chloride at 80°C was then used to convert the protected acid to the acid chloride 2 (mp 90-91°C).¹⁸ The product was recrystallized from hexane in 91% isolated yield. Alternatively, oxalyl chloride could be used with catalytic DMF to give 2 in 94% isolated yield. Spencer reported that aryl acid chlorides react with styrene under palladium(II) acetate catalysis with added base to give styrenes in good yield via a decarbonylative Heck-type process.¹⁹ This approach holds particular promise

in this case in that acid chloride 2 is readily made and the styrene coupling partner 3 is readily available and inexpensive. It was shown that the nature of the added base was critical for the success of the transformation. Added phosphine ligand inhibits the reaction giving greatly lowered yields. Non-coordinating amine bases, *N*-ethylmorpholine (NEM) and *N,N*-dimethylbenzylamine, proved optimal. Smaller amines capable of palladium coordination shift the equilibrium back in favor of carbon monoxide retention leading to lower stilbene formation.²⁰ Acetoxy substituted benzoyl chlorides were not explored previously. We recently reported the use of *N,N*-bis-(2,6-diisopropyl) dihydroimidazolium chloride 5 as a carbene-type ligand with palladium(II) acetate for efficient catalysis of Suzuki and Heck couplings with aryl diazonium ions.²¹ In these cases, added base was not required and product was formed in high yield. Using this catalyst (1 mol%), acid chloride 2 was coupled with styrene 3 (1.2 equiv.) with added *N*-ethylmorpholine in *p*-xylene at 120°C for 3.5 h. Following standard work-up and silica gel chromatography, resveratrol triacetate 6 (mp 116°C) was obtained in 73% yield. Resveratrol 1 was then obtained in pure form following basic hydrolysis in THF and acidification in 88% yield. The total overall yield was 53% requiring only four steps from resorcylic acid 4 performed on multigram scale.

Variations were explored using the methyl ether protected version of 2, together with changes in the amount of catalyst, ligand 5, and the use of other bases to form stilbene 6 (Table 1). With dimethyl ether 2 (*P*=Me) and 5 mol% palladium acetate, an extended reaction time of 18 h was needed to achieve a yield of 75%. *N,N*-Dimethylbenzylamine and Hünig's base gave lower yields. Diacetate acid chloride 2 (*P*=Ac) coupled with good reactivity using one mol% catalyst in less time, 3.5 h. When ligand 5 was left out, the product was obtained in lower yield, 63%. When the catalyst loading was lowered to 0.1 mol%, the yield again dropped to 57%. Use of *N*-methylmorpholine (NMM) was only



Scheme 2.

Table 1. Decarbonylative Heck coupling

P	Mol% Pd	Ligand	Base	Time (h)	Yield (%)
Me	5	—	NEM	18	75
Me	5	—	BnNMe ₃	18	52
Me	5	—	EtN(<i>i</i> -Pr) ₂	18	35
Ac	1	5	NEM	3.5	73
Ac	0.1	5	NEM	3.5	63
Ac	1	5	NMM	3.5	57
Ac	1	5	Et ₃ N	3.5	70
Ac	1	5	Et ₃ N	3.5	57

M. B. Andrus et al. / Tetrahedron Letters 44 (2003) 4819–4822

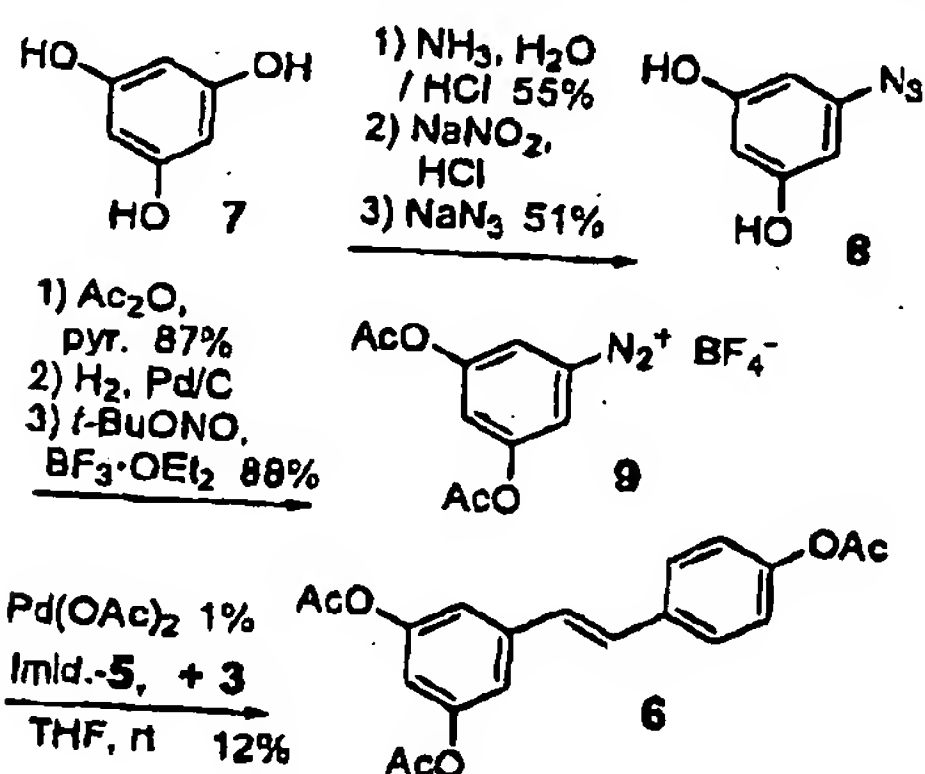
4821

slightly less effective, while added triethylamine gave product with lowered 57% yield.

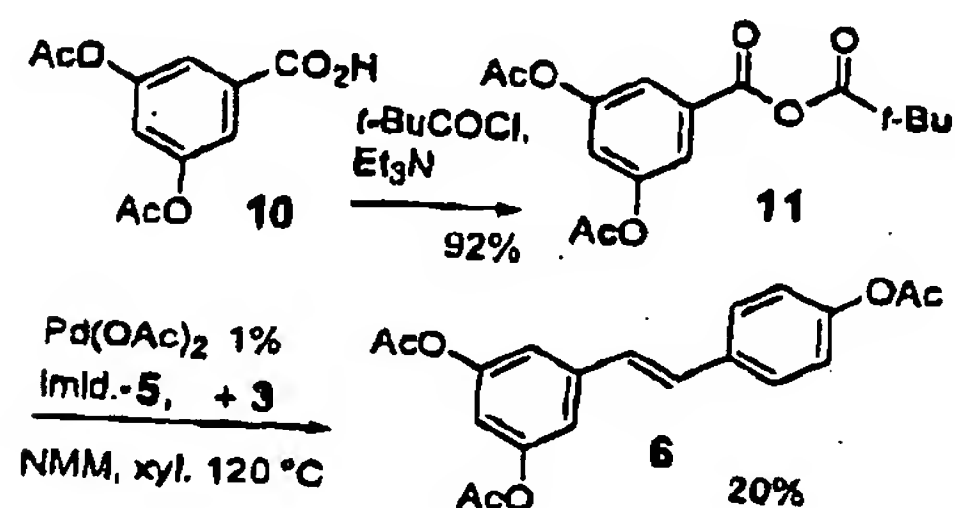
The efficiency of the decarbonylative Heck approach was compared to an aryl diazonium ion approach to **1** (Scheme 3).¹⁴ Phloroglucinol **7** was converted to 5-azido-1,3-recorsinol **8** using a three-step sequence.²² Acetate protection, aniline formation, and diazotization using *tert*-butyl nitrite, according to the procedure of Doyle, generated the aryl diazonium salt **9**.²³ Coupling of styrene **3** with the palladium acetate-imidazolium **5** catalyst gave product **6** in very low 12% isolated yield. The low efficiency of this coupling and the lengthy route to the aryl diazonium ion illustrate the superiority of the decarbonylative route.

Recently the decarbonylative Heck-type coupling has been extended to mixed anhydrides.²⁴ To explore this option, mixed anhydride **11** was formed from the protected acid **10** using pivaloyl chloride and triethylamine in 92% yield (Scheme 4).²⁵ Reaction under the coupling conditions with styrene **3** again gave low 20% yield of stilbene product **6**.

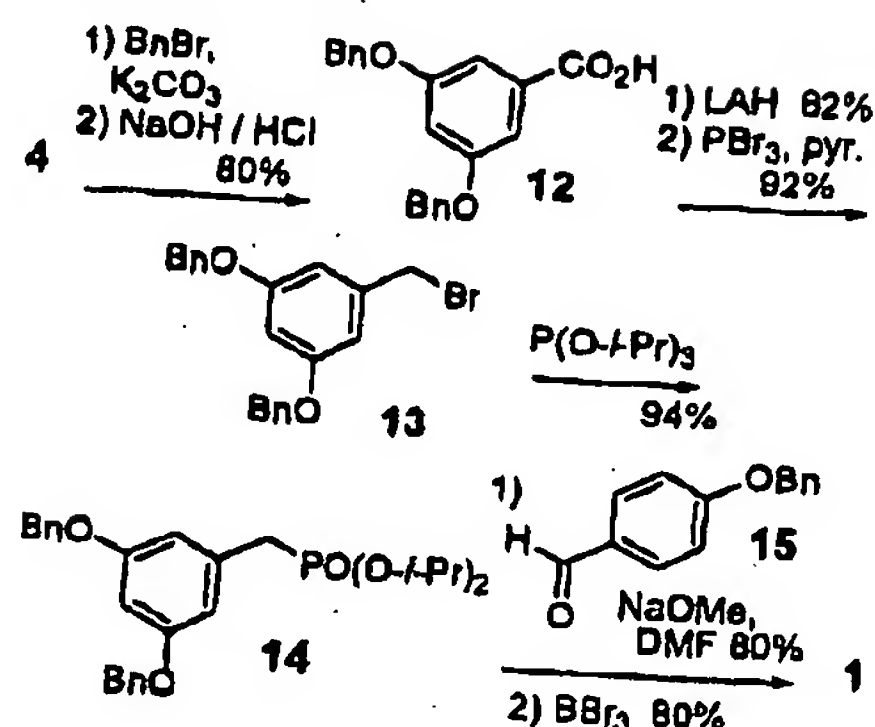
The decarbonylative route was also compared to an optimized Horner–Emmons based route using a diisopropyl phosphonate (Scheme 5). Resorcylic acid **4** was benzylated and hydrolyzed to give 3,5-dibenzyloxybenzoic acid **12** in good yield. Treatment with lithium aluminum hydride gave a benzyl alcohol that was then converted to benzyl bromide **13** using phosphorous tribromide. Arbuzov reaction with neat isopropyl phosphite produced phosphonate **14** in high yield. Coupling with 4-benzyloxybenzaldehyde **15** using sodium methoxide as base in DMF gave the protected stilbene in 80% yield. Boron tribromide was then used to give resveratrol **1**. The Horner–Emmons step using the diisopropyl phosphonate in this case gave only the *E*-stilbene in contrast to previous phosphonate routes that have produced mixtures.¹⁴ This route required seven steps and gave product in 36% overall yield.



Scheme 3.



Scheme 4.



Scheme 5.

oic acid **12** in good yield. Treatment with lithium aluminum hydride gave a benzyl alcohol that was then converted to benzyl bromide **13** using phosphorous tribromide. Arbuzov reaction with neat isopropyl phosphite produced phosphonate **14** in high yield. Coupling with 4-benzyloxybenzaldehyde **15** using sodium methoxide as base in DMF gave the protected stilbene in 80% yield. Boron tribromide was then used to give resveratrol **1**. The Horner–Emmons step using the diisopropyl phosphonate in this case gave only the *E*-stilbene in contrast to previous phosphonate routes that have produced mixtures.¹⁴ This route required seven steps and gave product in 36% overall yield.

The decarbonylative-Heck approach requires only four steps from inexpensive resorcylic acid and gives resveratrol in excellent 53% overall yield. The palladium catalyzed coupling allows for the use of acetate esters, which are easily removed. Aryl diazonium and mixed anhydride based routes are far less efficient. An improved Horner–Emmons synthesis is lower in overall yield and requires more steps.

Acknowledgements

We are grateful to The NIH (GM57275), The American Cancer Society, and BYU for funding, and Bruce Jackson for MS assistance.

References

- Gordon, M. H. *Nat. Prod. Rep.* 1996, 265–287.
- Gusman, J.; Malonne, H.; Atassi, G. *Carcinogenesis* 2001, 22, 1111–1117.
- Jung, D. S.; Kang, B. S.; Ryu, S. Y.; Chang, I. M.; Min, K. R.; Kim, Y. *Biochem. Pharmacol.* 1999, 57, 705–712.
- (a) Torres-Lopez, J. E.; Ortiz, M. I.; Castaneda-Hernandez, G.; Alonso-Lopez, R.; Asomoza-Espinosa, R.; Orandos-Soto, V. *Life Sci.* 2002, 70, 1669; (b) Tadolini, B.; Juliano, C.; Piu, L.; Franconi, F.; Cabrin, L. *Free Rad. Res.* 2000, 33, 105–114.

4822

M. B. Andrus et al. / *Tetrahedron Letters* 43 (2003) 4819-4822

5. Wang, Z. R.; Huang, Y. Z.; Zou, J. C.; Cao, K. J.; Xu, Y. N.; Wu, J. M. *Int. J. Mol. Med.* 2002, 9, 77-79.
6. (a) Jang, M.; Cai, L.; Udeani, G. O.; Slowing, K. V.; Thomas, C. F.; Beecher, C. W. W.; Fong, H. H. S.; Farnsworth, N. R.; Kinghorn, A. D.; Mentga, R. G.; Moon, R. C.; Pezzuto, J. M. *Science* 1997, 275, 218-220; (b) Savouret, J. F.; Quesne, M. *Blomed. Pharmacother.* 2002, 56, 84-87.
7. (a) Gupta, Y. K.; Chaudhary, G.; Srivastava, A. K. *Pharmacology* 2002, 65, 170-174; (b) Gupta, Y. K.; Briyal, S.; Chaudhary, G. *Pharmacol. Biochem. Behav.* 2002, 71, 245-249.
8. Docherty, J. J.; Fu, M. M. H.; Stiffler, B. S.; Limperos, R. J.; Pokabla, C. M.; DeLucia, A. L. *Antiviral Res.* 1999, 43, 145-155.
9. Renaud, S.; De Lorgeril, M. *Lancet* 1992, 339, 1523-1524.
10. Whitesell, L.; Minnaugh, E. G.; De Costa, B.; Myers, C. E.; Neckers, L. M. *Proc. Natl. Acad. Sci. USA* 1994, 91, 8324-8328.
11. Milner, J. A.; McDonald, S. S.; Anderson, D. E.; Greenwald, P. *Nutrition Cancer. Int. J.* 2001, 41, 1-16.
12. Chan, M. M. Y. *Biochem. Pharmacol.* 2002, 63, 99-104.
13. Romero-Perez, A. I.; Lamuela-Raventos, R. M.; Andres-Lacueva, C.; de La Torre-Boronat, M. C. *J. Agric. Food Chem.* 2001, 49, 210-215.
14. (a) Bachelor, F. W.; Loman, A. A.; Snowdon, L. R. *Can. J. Chem.* 1970, 48, 1554-1557; (b) Drewes, S. E.; Fletcher, I. P. *J. Chem. Soc., Perkin Trans. 2* 1974, 961-962; (c) Moreno-Manas, M.; Pleixats, R. *An. Quim., Ser. C* 1985, 81, 157-161; (d) Meier, H.; Dullweber, U. *Tetrahedron Lett.* 1996, 8, 1191-1194; (e) Orsini, F.; Pelizzoni, F.; Bellini, B.; Miglieri, G. *Carbohydr. Res.* 1997, 301, 95-109; (f) Alonso, E.; Ramon, D. J.; Yus, M. *J. Org. Chem.* 1997, 62, 417-421; (g) Orsini, F.; Pelizzoni, F.; Verotta, L.; Arburjai, T.; Rogers, C. B. *J. Nat. Prod.* 1997, 60, 1082-1087; (h) Shirai, R.; Takayama, H.; Nishikawa, A.; Koiso, Y.; Hashimoto, Y. *Bioorg. Med. Chem. Lett.* 1998, 8, 1997-2000; (i) Wang, M.; Jin, Y.; Ho, C.-T. *J. Agr. Food Chem.* 1999, 47, 3974-3977; (j) Eddarir, S.; Abdelhadi, Z.; Rolando, C. *Tetrahedron Lett.* 2001, 42, 9127-9130; (k) Petrit, G. R.; Grealish, M. P.; Jung, M. K.; Hamel, E.; Pettit, R. K.; Chapuis, J.-C.; Schmidt, J. M. *J. Med. Chem.* 2002, 45, 2534-2542; (l) Yu, J.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem.* 2002, 67, 4627-4629.
15. Guiso, M.; Marra, C.; Farina, A. *Tetrahedron Lett.* 2002, 43, 597-598.
16. Jeffery, T.; Ferber, B. *Tetrahedron Lett.* 2003, 44, 193-197.
17. (a) Al-Afaleq, E. I.; Abubshait, S. A. *Synth. Commun.* 1999, 29, 1965-1976; (b) Nagasaki, T.; Kimura, O.; Ukon, M.; Arimori, S.; Hamachi, I.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* 1994, 75-81; (c) Nagasaki, T.; Ukon, M.; Arimori, S.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* 1992, 608-610; (d) Burke, J. M.; Stevenson, R. *J. Chem. Res. Synth.* 1985, 34.
18. All compounds were adequately characterized by ¹H and ¹³C NMR and HR MS. Melting pts are noted for solid compounds.
19. (a) Blaser, H.-U.; Spencer, A. *J. Organomet. Chem.* 1982, 233, 267-272; (b) Spencer, A. *J. Organomet. Chem.* 1983, 247, 117-123; (c) Spencer, A. *J. Organomet. Chem.* 1984, 265, 323-329; (d) Spencer, A. *J. Organomet. Chem.* 1984, 270, 115-121.
20. Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* 2000, 100, 3009-3066.
21. (a) Andrus, M. B.; Song, C. *Org. Lett.* 2001, 3, 3761-3764; (b) Andrus, M. B.; Song, C.; Zhang, J. *Org. Lett.* 2002, 4, 2079-2082.
22. (a) Bockman, T. M.; Kosynkin, D.; Kochl, J. K. *J. Org. Chem.* 1997, 62, 5811-5820; (b) Richardson, S. K.; Jeganathan, A.; Mani, R. S.; Haley, B. E.; Watt, D. S. *Tetrahedron* 1987, 43, 2925-2934.
23. Doyle, M. P.; Siegfried, B.; Elliot, R. C.; Dellaria, J. F. *J. Org. Chem.* 1977, 42, 2431.
24. (a) Jeffery, T. *Tetrahedron* 1996, 52, 10113-10115; (b) Stephan, M. S.; Teunissen, A. J. J. M.; Verzijl, G. K. M.; de Vries, J. G. *Angew. Chem., Int. Ed.* 1998, 37, 662-664.
25. Gooben, L. J.; Ghosh, K. *Angew. Chem., Int. Ed.* 2001, 40, 3458-3460.

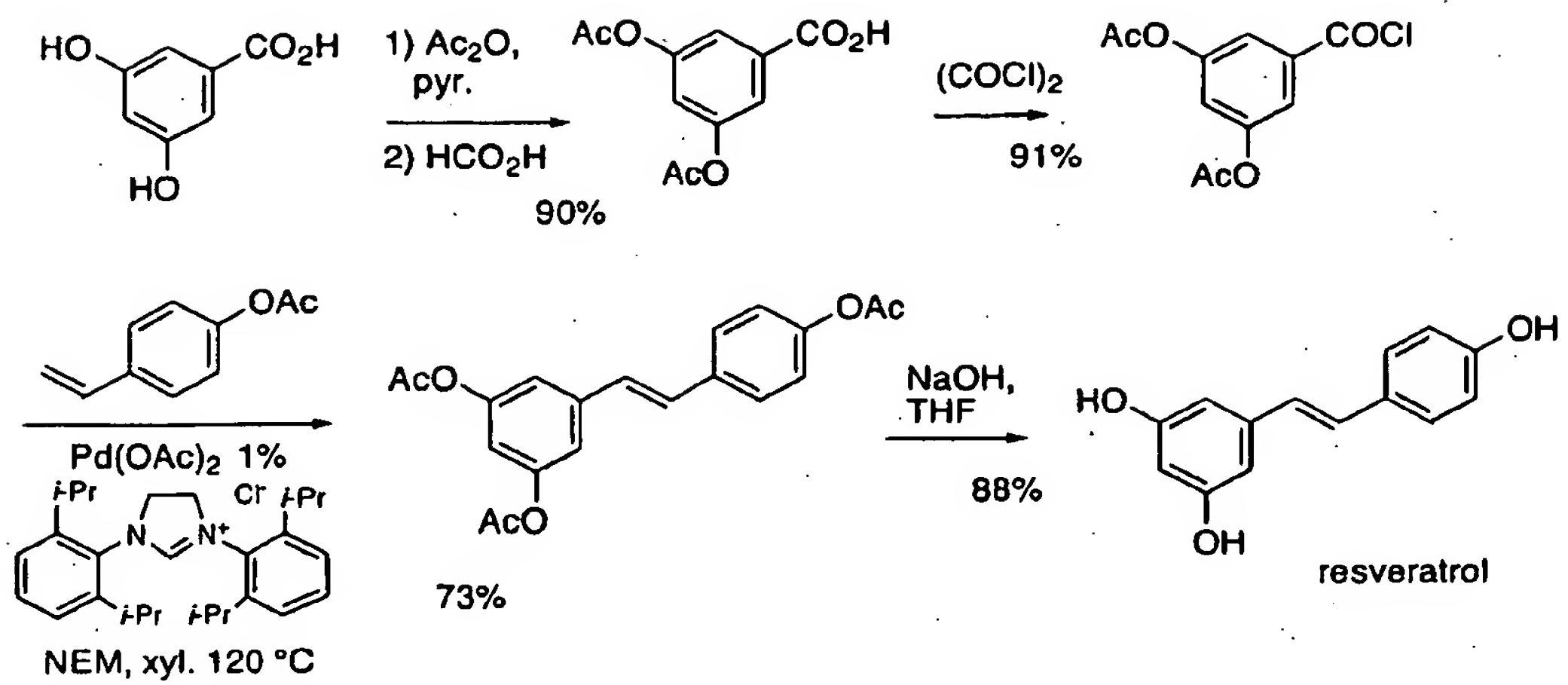


Figure 1

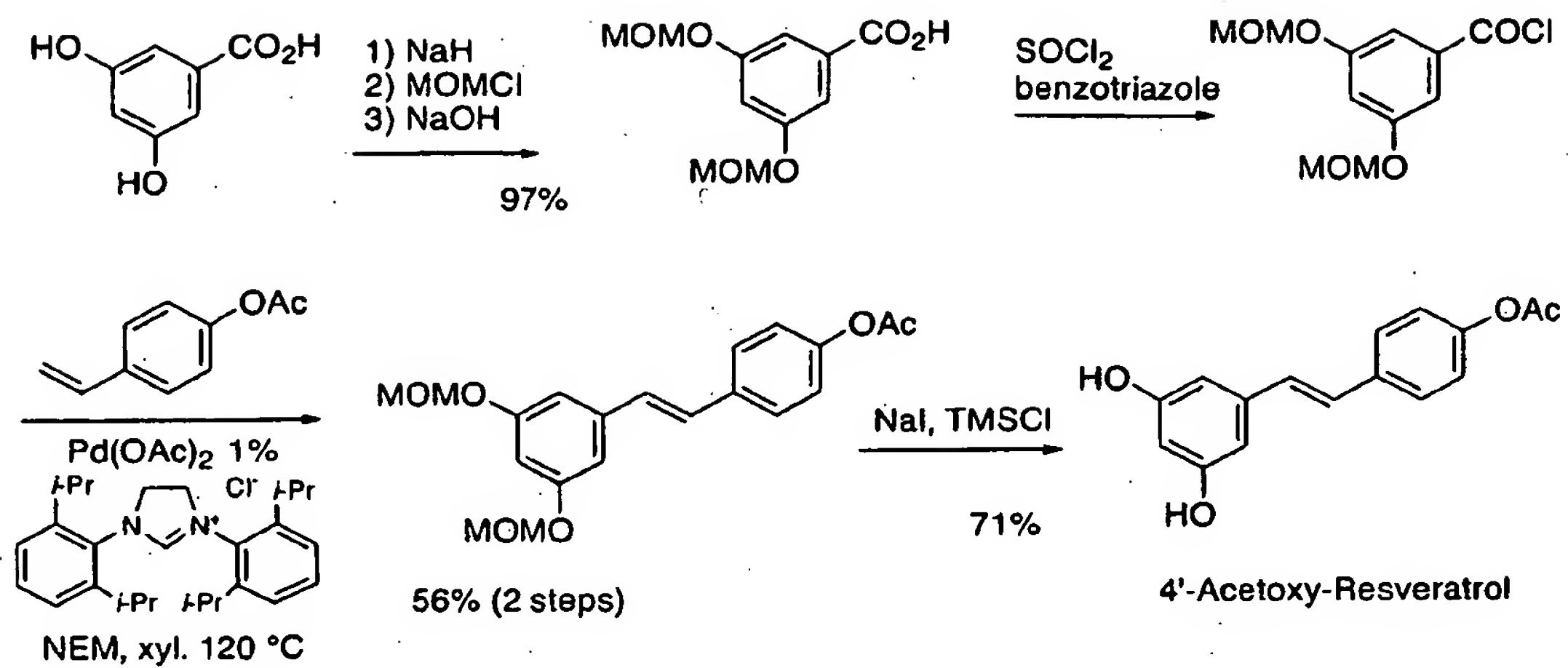


Figure 2

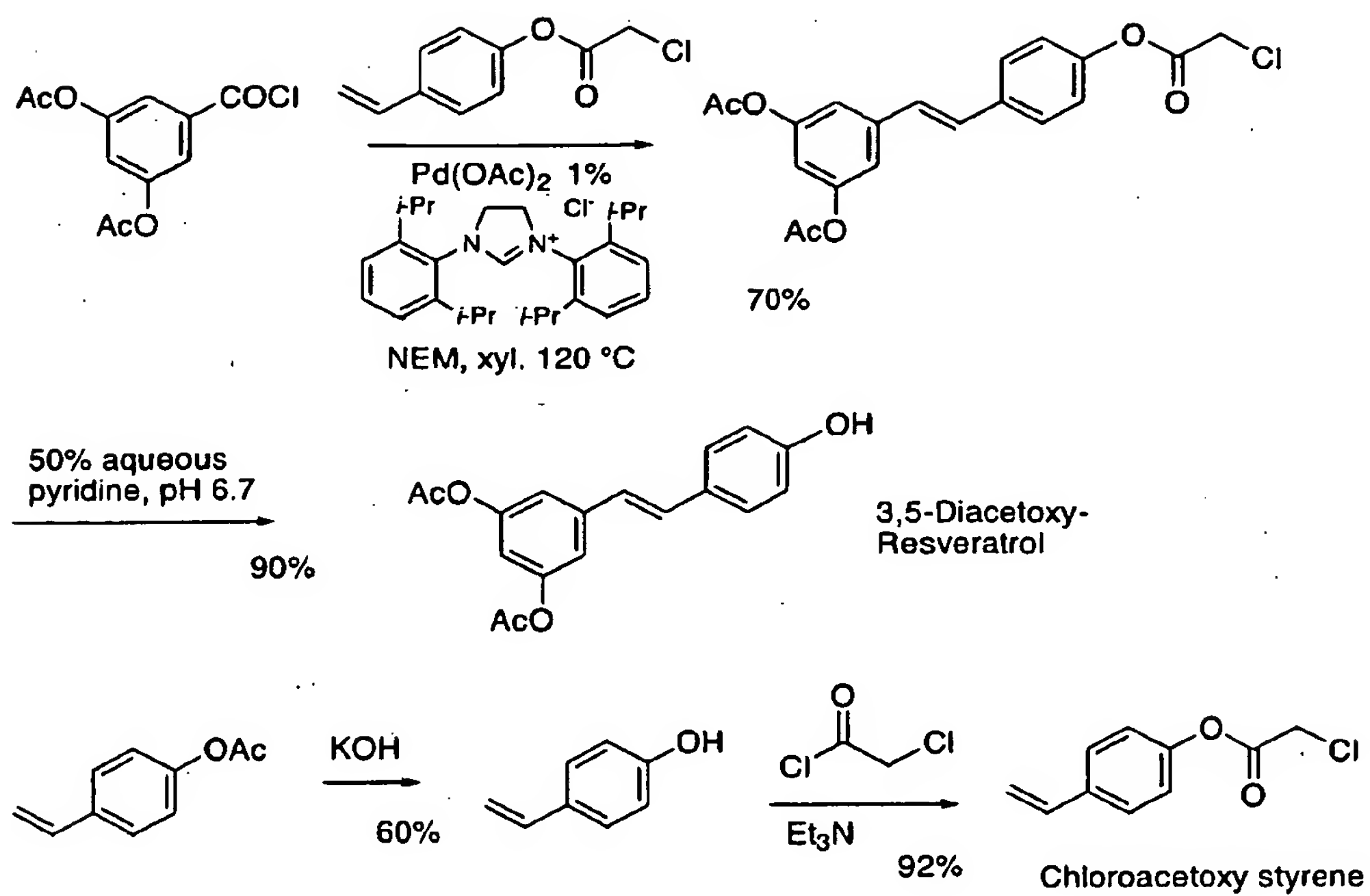


Figure 3

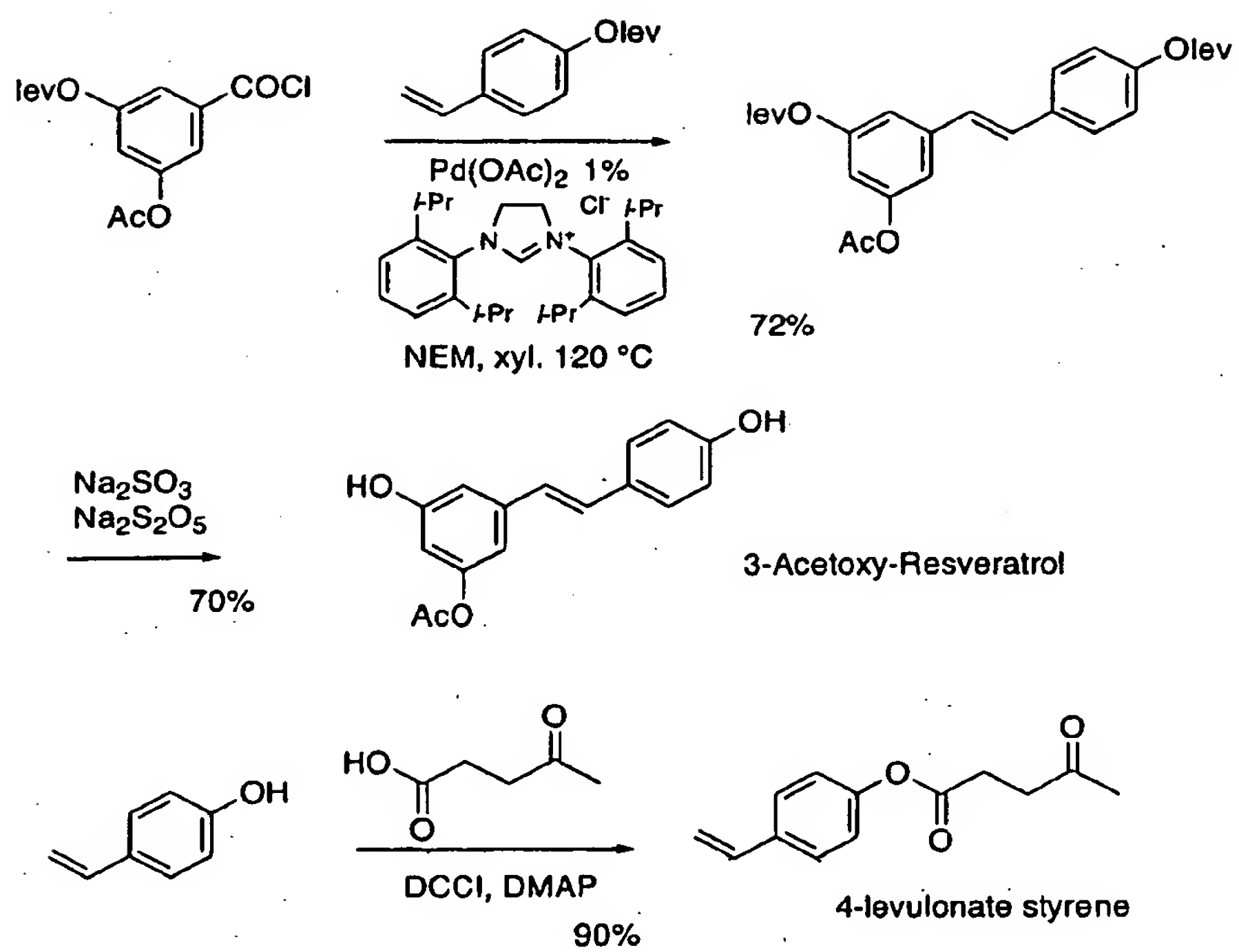


Figure 5

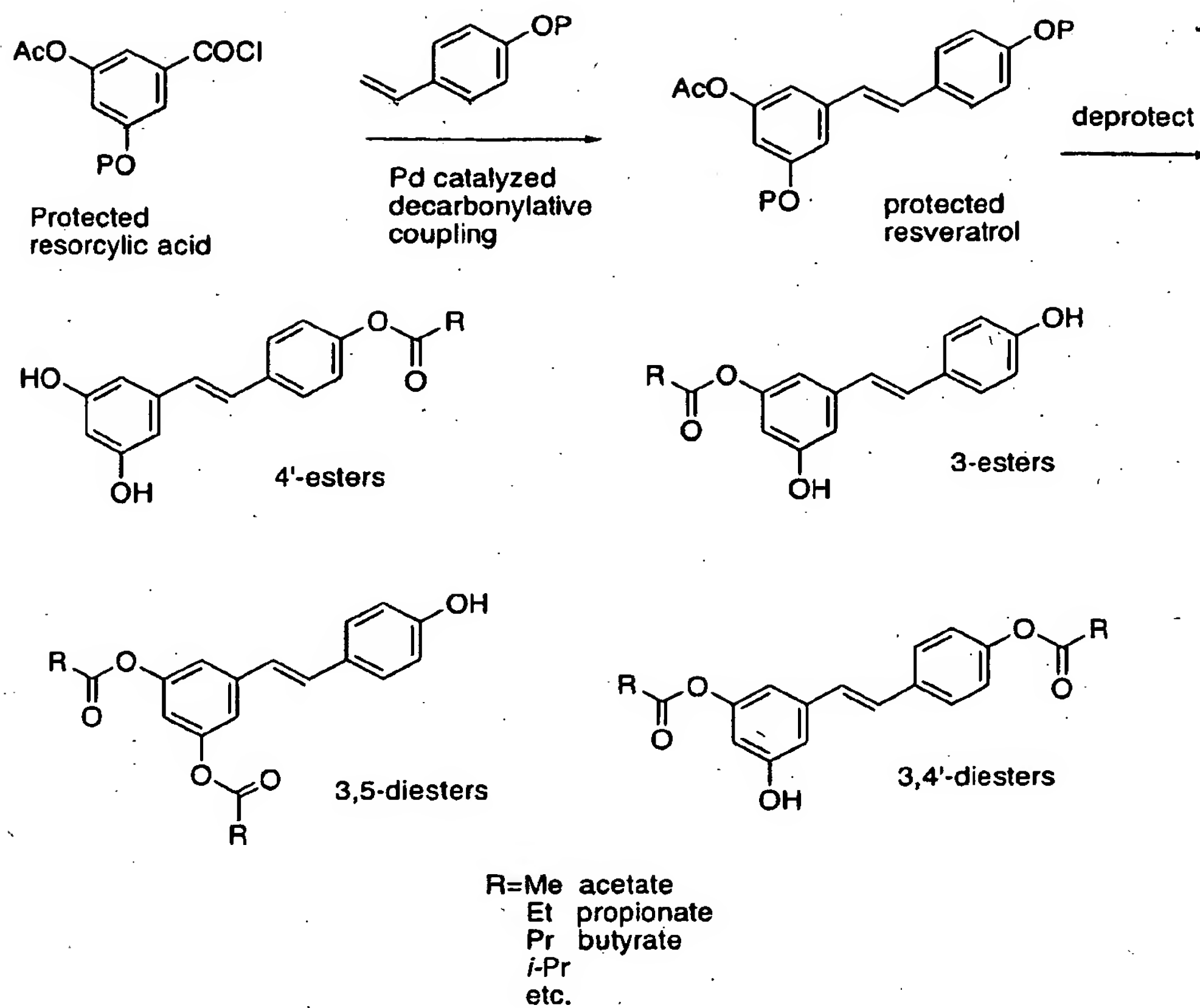


Figure 6